Cancer Pain Management: Current Guidelines and Research

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Goals and Objectives

1. Review the current approaches to effective cancer pain management
2. Discuss the challenges in delivering optimal pain management
3. Explore the development of new agents to treat pain

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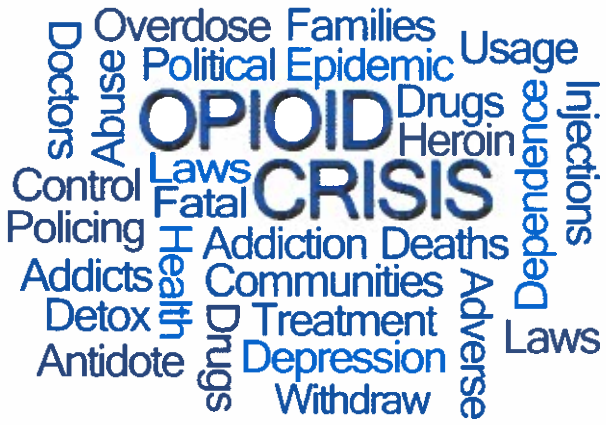

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Incidence of Pain in the Cancer Patient Population

- In advanced disease = 70%
- After curative treatment = 33%
- On anticancer treatment = 59%
- Pancreatic cancer = 44%
- Head and neck cancer = 40%
- Cancer survivors = 5 % to 10 %

Ann Oncol 2007;18:1437-1449

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Non-Tumor Related Pain

- Acute procedural pain
- Iatrogenic pain causes
- Comorbidity-related pain
- Pain in cancer survivors
  - Practice guideline: *J Clin Oncol 34:3325-3345, 2016*

Ann Oncol 2009;20: 1420-1433

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Assessment

- Assessment of pain descriptors can improve the choice of therapy (e.g. nociceptive vs neuropathic)
- Assessment scales: VAS, VRS, and NRS
- Assess and reassess the pain, the patient, and your ability to inform and communicate with the patient and family

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Principles of Pain Management

- Patients need to be educated about pain and pain management and take an active role in their pain management
- The onset of pain should be prevented by scheduled administration, taking into account the pharmacokinetics and pharmacodynamics of different drugs
- Analgesics for chronic pain should be prescribed on a regular basis, not as needed
- The oral route of administration should be the first choice

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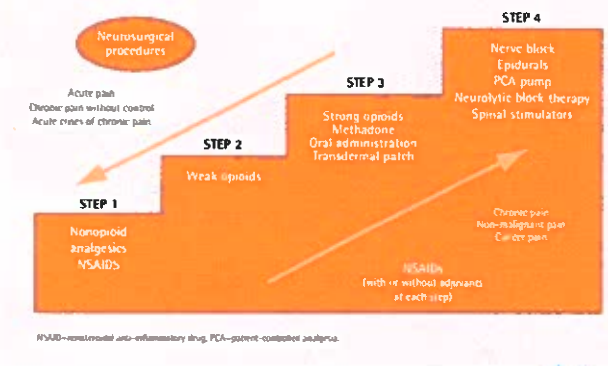
WHO Modified Ladder



NSAID—nonsteroidal anti-inflammatory drug, PCA—patient-controlled analgesia.

VOL 56: JU NE • JU IN 2010 Canadian Family Physician • Le Médecin de famille canadien

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Treatment of Mild Pain

- Acetaminophen – still a lack of knowledge regarding its effectiveness for cancer pain
- NSAID's – important to understand the risks of therapy
  - Including COX-2 selective inhibitors
- Based on a 2017 Cochrane review, there is no conclusive evidence to support or refute the use of NSAIDs alone or in combination with opioids for the treatment of cancer pain

Cochrane Database Syst Rev 2017;12: CD012638

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Treatment of Mild to Moderate Pain

- Few options before moving to strong opioids
- This is where controversy on step 2 of the WHO pain ladder comes into play
  - ? Elimination and move to low dose morphine
- Tramadol
  - Can have significant side effects
  - Reduced effect in poor metabolizers P450 2D6
  - Affects serotonin metabolism and availability, lowering seizure threshold in the elderly
- Dihydrocodeine
- Codeine
- Any of the above can be given in combination with non-opioid analgesics

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Treatment of Moderate to Severe Pain (1/2)

- The opioid of first choice for moderate to severe pain is oral morphine
- The average relative potency ratio of oral to i.v. morphine is between 1:2 and 1:3
- Oxycodone or hydromorphone, and oral methadone are affective alternatives to oral morphine
- Transdermal fentanyl and buprenorphine best suited for patients with stable opioid requirements, safe in chronic kidney disease
- Methadone

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Treatment of Moderate to Severe Pain (2/2)

- Opioid switching
- A different opioid should be considered in the absence of adequate analgesia or in the presence of unacceptable opioid side effects
- SC route simple and effective and should be used when patients cannot take opioids by the oral or t.d. route
- I.V. infusion should be considered when s.c. administration is contraindicated or for opioid titration when rapid pain control is needed

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Opioid Conversion Table

Calculating Morphine Milligram Equivalents (MME)			
Opioid	Conversion Factor (convert to MMEs)	Duration (hours)	Dose Equivalent Morphine Sulfate 30 mg
Codeine	0.15	4-6	200 mg
Fentanyl (mcg/hr)	2.4		12.5 mcg/hr
Hydrocodone	1	3-6	30 mg
Hydromorphone	4	4-5	7.5 mg
Morphine	1	3-6	30 mg
Oxycodone	1.5	4-6	20 mg
Oxymorphone	3	3-6	10 mg
Methadone			
1-20 mg/day	4		7.5
21-40 mg/day	8		3.75
41-60 mg/day	10		3 mg
≥61 mg/day	12		2.5 mg

https://www.cdc.gov/drugoverdose/pdf/calculating_total_daily_dose-a.pdf

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Sample Conversion Case

Your patient is a 50-year old man who is taking oxymorphone 10 mg 4 times a day for chronic pain
You determine he is an appropriate candidate for a long-acting regimen and decide to convert him to extended release oxycodone

1. Total daily dose of oxymorphone → 10 mg x 4 times/day = 40 mg/day
2. Convert to MMEs (oxymorphone conversion factor = 3) → 40 x 3 = 120 MME
3. Determine MMEs of oxycodone (oxycodone conversion factor = 1.5) → 120/1.5 = 80 mg/day
4. Decrease dose by 25% → 25% of 80 = 20 → 80 – 20 = 60
5. Divide by interval (q 12 hours) → 60/2 = 30

The starting dose of extended release oxycodone is 30 mg every 12 hours

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Management of Opioid Side Effects

- Laxatives must be routinely prescribed for the management and prophylaxis of OIC
- The use of naloxone in association with oxycodone or methylnaltrexone to control OIC may be considered
- Metoclopramide and antidopaminergic drugs should be recommended for opioid-related nausea and vomiting
- Psychostimulants (e.g. methylphenidate) to treat opioid-induced sedation only when other methods fail
- Mu receptor antagonists (e.g. naloxone) should be used promptly to reverse respiratory depression caused by opioids

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Bone Pain

- Treatment of bone pain should always take into consideration the use of analgesic agents
- All patients with painful bone metastases should be offered external beam radiation therapy at a dose of 8 Gy in a single dose
- Patients with recurrent bone pain after previous irradiation should be offered another dose
- Stereotactic body radiation therapy is a newer option that allows administration of higher doses while avoiding high doses to critical normal tissues

Lancet Oncol 2014; 15: 164-171

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Cancer-Related Neuropathic Pain (NP)

- NP is a direct consequence of a cancer-induced injury to the somatosensory system
- Must differentiate from other NPs (e.g. cancer treatment)
- Cancer-related NP can be treated using opioids in combination with carefully dosed adjuvants
- Patients with NP should be given a TCA or anticonvulsant and monitored for side effects
- Gabapentin, pregabalin, duloxetine, and TCA (doses < 75 mg/day) are strongly recommended as first line agents for NP

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Breakthrough Cancer Pain (BTcP)

- No consensus on the definition and characteristics of BTcP
- Major gap in knowledge of non-opioids and non-pharmacological approaches to BTcP
- Immediate-release opioids should be used to treat BTcP responsive to opioids
- Transmucosal fentanyl formulations have a role in unpredictable and rapid-onset BTcP

Curr Med Res Opin 2012; 28: 859-870

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Invasive Management of Refractory Pain

- Intrathecal drug delivery
- Peripheral nerve block
- Neurolytic blockade
- Neurolysis of coeliac plexus
- Cordotomy for cancer-related pain

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End-of-Life-Pain

- 53% to 70% of patients require an alternative route for opioid administration in the months and hours before death
- Pain can be accompanied by other symptoms which can exacerbate underlying central pain mechanisms
- Careful assessment of physical pain and total suffering required
- Sedation may be an option after all possible causes of suffering have been addressed by a multidisciplinary team
- Opioid-induced hypersensitivity must also be kept in mind

Annals of Oncology 29 (Supplement 4): iv166-iv191, 2018

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Challenges to the Delivery of Effective Pain Management

- Stigma surrounding the use of opioids
- Providers faced with balancing the risks of opioid abuse and of inadequate pain management treatment
- Illicit opioids, rather than prescription opioids, may be a more significant issue
- Opioid Phobia
- Manufacturers do not have incentives to create alternative treatments
- **New Opioid Crisis – Patients with legitimate pain that require opioids are having a hard time accessing them**

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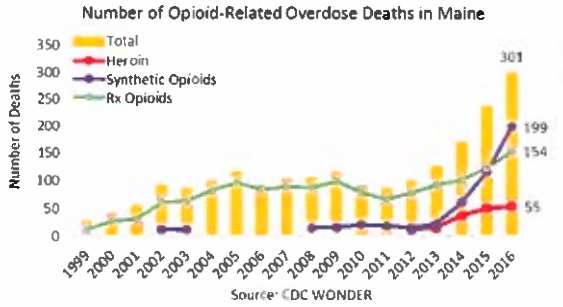
Opioid-Related Deaths in Maine



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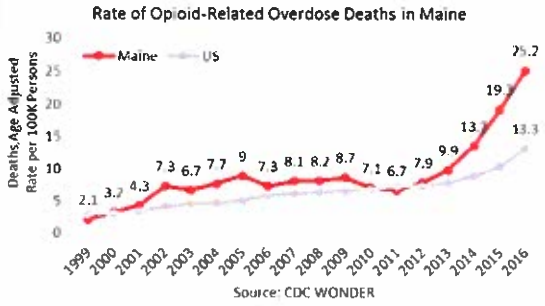
Rate of Opioid Deaths in Maine



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New Non-Opioid Drugs in Development (1/2)

- Biopharma companies face a multifaceted problem
  - Understanding the science of pain
  - Discovering new biological targets
  - Identifying biomarkers as endpoints for efficacy
  - Trial design changes to improve chances of success
  - Willingness of health care providers and insurers to pay for new alternatives when they reach the market
  - Pain, unlike other disease endpoints is completely subjective
  - Drugs do not get developed unless there is a financial incentive to do so

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New Non-Opioid Drugs in Development (2/2)

- ML351 – designed to inhibit the naturally produced enzyme 15-Lipoxygenase-1 which synthesizes bioactive lipids that contribute to pain not relieved by common anti-inflammatory agents such as ibuprofen
- α9/α10 nicotinic acetylcholine receptor (nAChR) antagonist derived from the venom of the *Conus regius,* s small cone snail native to the Caribbean Sea – anti-inflammatory and neuroprotective effects
- Transient receptor potential (TRP) ion channel family of small molecule inhibitors (TRP1) – target is located in the peripheral nervous system on the endings of specialized nociceptor nerve fibers
- Other drugs being developed are targeting cannabinoid receptors, nerve growth factor (NGF) receptors, G-protein coupled receptors (GPCRs) and calcitonin gene-related peptides (CGRPs)

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Summary

- Overall, the basic concepts of effective pain management have not changed
- There are newer versions of older opioids on the market, some designed to mitigate opioid misuse
- Assessment and reassessment along with patient education are cornerstones of success in treating cancer-related pain
- The "opioid crisis" has created challenges for effective pain management delivery
- In the years to come, we may have newer agents that can control pain without the side effects and abuse potential

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